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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,325	GLEAVE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/02 2&3/03 4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group IV in the reply filed on September 24, 2004 is acknowledged. Pursuant to the agreement reached between examiner Lacourciere and applicant with regard to SEQ ID NOS: 4, 5 and 12 in this application groups IV-VI have been rejoined and all claims drawn to these three sequences will be examined. Additionally, upon further consideration it is noted that groups I-III are also drawn to SEQ ID NOS: 4, 5 and 12 and the active method step of each of inventions I-III is the same as those in groups IV-VI; administering a composition that is an antisense compound to an individual to inhibit expression of TRPM-2. Since the active step in these methods is the same, groups I-III have also been rejoined. However, if the claims are later amended so as to make the active method steps divergent, the restriction requirement between groups I-III and IV-VI may be reinstated.

Claims 1-34 are pending in the application and will be examined on the merits.

Specification

1. The abstract of the disclosure is objected to because of excessive length. The abstract should not contain more than 150 words. Correction is required. See MPEP § 608.01(b).

Claim Objections

2. Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 19 is dependent upon claims 12, 8 and 7. The limitation of claim 19 is identical to that of claim 7 and since claims 8 and 12 already contain this limitation claim 19 does not further limit claim 12.

3. Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 20 is dependent upon claims 13, 12 and 8. The limitation of claim 20 is identical to that of claim 8 and since claims 12 and 13 already contain this limitation claim 20 does not further limit claim 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 21-23 each recite the limitation "wherein the antisense oligonucleotide has the sequence..." and are each dependent on claim 14. Claim 14 is drawn to the method of claim 8, treating prostate cancer in an individual using an antisense oligonucleotide, and contains the limitation of performing the method of claim 8 with the further step of providing a second antisense oligonucleotide that inhibits expression of an anti-apoptotic protein other than TRPM-2. In claims 21-23 it is unclear what antisense oligonucleotide is being referred to by the limitation "wherein the antisense oligonucleotide has the sequence..." Is it the antisense from claim 8 or the second antisense referred to in claim 14, the immediate parent claim of claims 21-23? For the purposes of examination this limitation is being interpreted as referring to the first antisense oligonucleotide recited in claim 8.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-8, 12-25, 30, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

5. Claim 1 is drawn to a method of delaying the progression of prostatic tumor cells to an androgen-independent form by administering an antisense oligonucleotide that inhibits expression of TRPM-2. Claim 2 limits claim 1 by stating that the antisense oligonucleotide is targeted to the translation initiation or termination site of the TRPM-2 mRNA. Claim 6 is drawn to a method of treating prostrate cancer by inducing apoptosis through initiation of androgen-withdrawal and then administering an agent that inhibits expression of TRPM-2. Claims 7 and 8 limit claim 6 by stating that the inhibitory agent can be an antisense oligonucleotide that may be targeted to the translation initiation or termination site. Claims 12 and 13 limit claim 8 by stating that the method of treating the cancer with an antisense oligonucleotide can be used in combination with other chemotherapeutic agents. Claims 19 and 20 limit claims 12 and 13, respectively, by stating the method is performed with an antisense oligonucleotide. Claims 14-17 limit claim 8 by stating that the method of treating the cancer with an antisense oligonucleotide can be used in combination with a second antisense that inhibits another anti-apoptotic protein, possibly in combination with other chemotherapeutic

agents. Claims 21-23 limit claim 14 by reciting the sequence of the antisense oligonucleotide. Claims 30, 32 and 34 limit claims 9, 10 and 11, respectively, by stating that the method of treating the cancer with the claimed antisense oligonucleotide sequences can be used in combination with a second antisense that inhibits another anti-apoptotic protein. Claim 18 is drawn to a method of enhancing the chemo- or radiation-sensitivity of cancer cells using a composition that inhibits expression of TRPM-2. Claims 24 and 25 are drawn to a method of delaying progression of a population of prostatic cancer cells from a state of androgen sensitivity to an androgen independent state by inhibiting TRPM-2 expression with an antisense oligonucleotide that may be directed to the translation initiation or termination site.

6. The specification teaches on page 3 that the inventors have discovered that antisense therapy that reduces expression of TRPM-2 provides therapeutic benefits in the treatment of cancer and that TRPM-2 antisense oligonucleotides are effective at delaying onset of androgen independence in prostatic tumor cell *in vivo*. On pages 8 and 9 modifications to the antisense oligonucleotides and possible methods of administration are contemplated. Example 1 of the instant specification teaches that antisense oligonucleotides directed to TRPM-2 cause greater regression of Shionogi tumors in mice than a mismatched oligonucleotide. Further examples in the specification teach the use of antisense oligonucleotides to inhibit TPRM-2 alone or in combination with an antisense oligonucleotide directed toward Bcl-2 as well as other chemotherapies including paclitaxel, mitoxanthrone and radiation in human cancer cells

in vitro. *In vivo* experiments in mice were conducted using antisense oligonucleotides to TRPM-2 in combination with chemotherapeutic agents paclitaxel and mitoxanthrone.

7. The instant specification discloses the sequences of 14 antisense oligonucleotides: eleven targeted to TRPM-2, one targeted to Bcl-2 and 2 mismatch controls. No specific description is provided on how to use the claimed methods to delay progression of prostatic tumor cells, to enhance chemo- or radiation sensitivity of a cancer cell or to treat cancer using antisense oligonucleotides to TRPM-2 in any organism other than the mouse.

8. Claims 6 and 18 encompass the use of any inhibitor of TRPM-2 expression to treat cancer or to enhance the chemo- or radiation sensitivity of a cancer cell, including inhibitors that are nucleic acids that are not antisense inhibitors such as double stranded RNAs that act by RNA interference and non-nucleic acid inhibitors such as proteins or small molecules and inhibitors of TRPM-2 that are not nucleic acids. The encompassed genus of inhibitors of TRPM-2 that are either nucleic acid or non-nucleic acid inhibitors that could be used in the claimed method is very large. Claims 14, 15, 30, 32 and 34 encompass the use of any antisense sequence targeted to any region of a gene encoding any anti-apoptotic protein that is not TRPM-2. The sequences of 11 oligonucleotides disclosed as antisense to TRPM-2 and the single sequence disclosed as antisense to Bcl-2 are not representative of even the full breadth of antisense inhibitors of TRPM-2 or any other gene encoding any anti-apoptotic protein that is not TRPM-2, much less the full breadth of the genus of other nucleic acid and non-nucleic acid compounds that could be used to perform the claimed methods. Inhibitors of a

particular gene must be determined empirically; the structures provided do not share a common structure that has been shown in the instant application or is known in the art to impart a particular function. For example, there is no description of the structure of other nucleic acid inhibitors of TRPM-2 nor is there any description of the structures of any non-nucleic acid inhibitors of TRPM-2. Aside from the single antisense sequence directed to Bcl-2, there is no description of any antisense sequences to anti-apoptotic proteins other than TRPM-2. The 14 sequences provided do not serve to describe these embodiments of the genus of inhibitors of TRPM-2 or Bcl-2 or all other anti-apoptotic proteins that are encompassed by the instant claims.

9. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

10. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not

disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

11. With the exception of the antisense sequences disclosed in the specification, the skilled artisan cannot envision the detailed structure of the encompassed antisense sequences to TRPM-2 or the detailed structure of the encompassed antisense sequences to Bcl-2 or the detailed structure of the encompassed antisense sequences to any other anti-apoptotic proteins or the encompassed nucleic acid inhibitors of TRPM-2 that are not antisense inhibitors that could be used in the claimed method. Also, the skilled artisan can not envision the detailed structure of the encompassed inhibitors of TRPM-2 that are not nucleic acids that could be used in the claimed method, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

12. Therefore, only the disclosed antisense sequences, but not the full breadth of inhibitors of TRPM-2 that could be used in the claimed methods meet the written description provision of 35 USC 112, first paragraph. Only the single disclosed antisense sequence to Bcl-2 but not the full genus of antisense oligonucleotides targeted to all anti-apoptotic proteins that are not TRPM-2 meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 1, 2, 6-8, 12-25, 30, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of antisense oligonucleotides to TRPM-2 alone or in combination with other chemotherapeutic agents *in vitro* or *in vivo* in the mouse, does not reasonably provide enablement for use of antisense oligonucleotides to TRPM-2 alone or in combination with other chemotherapeutic agents, including antisense oligonucleotides to other anti-apoptotic proteins than TRPM-2, to treat cancer in any other animal, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a

disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

13. Claim 1 is drawn to a method of delaying the progression of prostatic tumor cells to an androgen-independent form *in vivo* by administering an agent that inhibits expression of TRPM-2. Claim 2 limits claim 1 by stating that the inhibitory agent can be an antisense oligonucleotide that may be targeted to the translation initiation or termination site. Claim 6 is drawn to a method of treating prostrate cancer by inducing apoptosis through initiation of androgen-withdrawal and then administering an agent that inhibits expression of TRPM-2. Claims 7 and 8 limit claim 6 by stating that the inhibitory agent can be an antisense oligonucleotide that may be targeted to the translation initiation or termination site. Claims 12 and 13 limit claim 8 by stating that the method of treating the cancer with an antisense oligonucleotide can be used in combination with other chemotherapeutic agents. Claims 19 and 20 limit claims 12 and 13, respectively, by stating the method is performed with an antisense oligonucleotide. Claims 14-17 limit claim 8 by stating that the method of treating the cancer with an antisense oligonucleotide can be used in combination with a second antisense that inhibits another anti-apoptotic protein, possibly in combination with other chemotherapeutic agents. Claims 21-23 limit claim 14 by reciting the sequence of the antisense oligonucleotide. Claim 18 is drawn to a method of enhancing the chemo- or

radiation-sensitivity of cancer cells using a composition that inhibits expression of TRPM-2. Claims 24 and 25 are drawn to a method of delaying progression of a population of prostatic cancer cells from a state of androgen sensitivity to an androgen independent state by inhibiting TRPM-2 expression with an antisense oligonucleotide that may be directed to the translation initiation or termination site.

14. The specification teaches on page 3 that the inventors have discovered that antisense therapy that reduces expression of TRPM-2 provides therapeutic benefits in the treatment of cancer and that TRPM-2 antisense oligonucleotides are effective at delaying onset of androgen independence in prostatic tumor cell *in vivo*. On pages 8 and 9 modifications to the antisense oligonucleotides and possible methods of administration are contemplated. Example 1 of the instant specification teaches that antisense oligonucleotides directed to TRPM-2 cause greater regression of Shionogi tumors in mice than a mismatched oligonucleotide. Further examples in the specification teach the use of antisense oligonucleotides to inhibit TPRM-2 alone or in combination with an antisense oligonucleotide directed toward Bcl-2 as well as other chemotherapies including paclitaxel, mitoxanthrone and radiation in human cancer cells in vitro. *In vivo* experiments in mice were conducted using antisense oligonucleotides to TRPM-2 in combination with chemotherapeutic agents paclitaxel and mitoxanthrone.

15. The specification teaches on pages 8 and 9 that antisense oligonucleotides can be modified to increase the stability of the oligonucleotide *in vivo* and that delivery methods and amounts used are known in the art. No specific guidance is provided on how to use the claimed methods to delay progression of prostatic tumor cells to an

androgen independent state, to enhance chemo- or radiation sensitivity of a cancer cell or to treat cancer using antisense oligonucleotides to TRPM-2 in any organism other than mice. No specific guidance is provided on how to used the claimed methods to treat cancer using antisense oligonucleotides to TRPM-2 in combination with antisense oligonucleotides to any other anti-apoptotic protein and/or other chemotherapeutic agents in any organism other than mice.

16. The state of the art prior art is such that antisense inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression using antisense oligonucleotides at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

17. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 45-50), and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

18. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of

delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

19. Crooke, (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

20. Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have

indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

21. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples in human cancer cell lines and *in vivo* examples in mice, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

22. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of

expression of TRPM-2 or any other anti-apoptotic protein in cancer cells to a therapeutically significant extent. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

23. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene.

24. The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

25. Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of delaying the progression of prostatic tumor cells to an androgen independent state, treating cancer or enhancing the chemo- or radiation sensitivity of cancer cells in all organisms as the art of inhibiting gene expression by introducing antisense oligonucleotides into an

organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences capable of binding to TRPM-2 and what antisense sequences would actually bind to TRPM-2 and form a strong enough complex that they would be effective at inhibiting expression of TRPM-2, 2). determining the sequences of all genes encoding all other anti-apoptotic proteins and then determining what sequences would constitute antisense sequences capable of binding to the genes encoding these other anti-apoptotic proteins and what antisense sequences would actually bind to these genes and form a strong enough complex that they would be effective at inhibiting expression of the genes encoding all other anti-apoptotic proteins 3). the form of the antisense oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 4). the mode of delivery of the antisense oligonucleotide to an organism that would allow it to reach the targeted cell, 5). the amount of antisense oligonucleotide that would need to be delivered in order to bind a sufficient amount of TRPM-2 or any other gene encoding any other anti-apoptotic protein and inhibit expression of the target gene once it reached the proper cell and 6). ensuring the antisense oligonucleotide remains viable in a cell for a period of time that allows inhibition of expression of TRPM-2 or any other gene encoding any other anti-apoptotic protein to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of

experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1, 2, 6-8, 12-20, 24 and 25 are not enabled.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

26. Claim 18 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 09/967,726. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 1, 3, 6, 9, 14, 15, 18, 21, 24, 26, 29 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4, 6, 10 and 11 of copending Application No. 10/080,794. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 2 of the '794 application is fully encompassed within claims 1 and 3 of the instant Application, claim 3 of the '794 application is fully encompassed

within claims 6 and 9 of the instant Application, claim 4 of the '794 application is fully encompassed within claim 29 of the instant Application, claim 6 of the '794 application is fully encompassed within claims 14, 15, 21 and 30 of the instant Application, claim 10 of the '794 application is fully encompassed within claim 18 of the instant Application and claim 11 of the '794 application is fully encompassed within claims 24 and 26 of the instant Application.

28. Claims 1-11, 18 and 24-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 9 of copending Application No. 10/646,391. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 and 9 of the '391 application are drawn to methods of treating melanoma using an agent that reduces the amount of clusterin in a cancer cell wherein the agent can be antisense oligonucleotides and the antisense nucleotides can be any of those designated as SEQ ID NOS: 2-19 in the '391 application. Claims 1-11, 18 and 24-28 of the instant Application are drawn to methods of delaying the progression of prostatic tumor cells, methods of treating cancer and methods of enhancing chemo- or radiation sensitivity of a cancer by administering a composition that inhibits expression of TRPM-2, which is another name for clusterin, thus reducing the amount of TRPM-2/clusterin in the cell wherein the inhibitor of TRPM-2/clusterin can be antisense oligonucleotides. The active method step of each of these methods is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat melanoma and enhance the chemo- or radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the

instant Application are also claimed in the '391 application. Claims 29-34 of the instant application are drawn to a method of treating prostate cancer using SEQ ID NOS: 4, 5 or 12 in combination with either a chemotherapy agent or a second antisense sequence targeted to an anti-apoptotic protein other than TRPM-2. These claims are drawn to an inventions that are an obvious modification of claims 1-3 and 9 of the '391 application. Section 2144.06 of the MPEP states the following in the context of "art recognized equivalence for the same purpose":

> "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

29. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

30. Claims 1-11, 18 and 24-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-8 of copending Application No. 10/828,394. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 and 6-8 of the '394 application are drawn to methods for treatment of a cancerous angiogenesis-related disease or reducing angiogenesis in a cancerous angiogenesis-related disease using an agent that reduces the amount of clusterin in a cancer cell wherein the agent can be antisense oligonucleotides. Claims 1-11, 18 and 24-28 of the instant Application are drawn to methods of delaying the progression of prostatic tumor cells, methods of treating cancer and methods of enhancing chemo- or radiation sensitivity of a cancer by administering a composition that inhibits expression of TRPM-

2, which is another name for clusterin, thus reducing the amount of TRPM-2/clusterin in the cell wherein the inhibitor of TRPM-2/clusterin can be antisense oligonucleotides. The active method step of each of these methods is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat a cancerous angiogenesis-related disease or reduce angiogenesis in a cancerous angiogenesis-related disease and enhance the chemo- or radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the instant Application are also claimed in the '394 application. Claims 29-34 of the instant application are drawn to a method of treating prostate cancer using SEQ ID NOS: 4, 5 or 12 in combination with either a chemotherapy agent or a second antisense sequence targeted to an anti-apoptotic protein other than TRPM-2. These claims are drawn to an inventions that are an obvious modification of claims 1-3 and 9 of the '394 application. Section 2144.06 of the MPEP states the following in the context of "art recognized equivalence for the same purpose":

> "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

31. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 1-11, 18 and 24-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-8 of copending Application No. 10/828,395. Although the conflicting claims are

not identical, they are not patentably distinct from each other because claims 1-3 and 6-8 of the '395 application are drawn to methods for treatment of a non-cancerous angiogenesis-related disease or reducing angiogenesis in a non-cancerous angiogenesis-related disease using an agent that reduces the amount of clusterin in a cancer cell wherein the agent can be antisense oligonucleotides. Claims 1-11, 18 and 24-28 of the instant Application are drawn to methods of delaying the progression of prostatic tumor cells, methods of treating cancer and methods of enhancing chemo- or radiation sensitivity of a cancer by administering a composition that inhibits expression of TRPM-2, which is another name for clusterin, thus reducing the amount of TRPM-2/clusterin in the cell wherein the inhibitor of TRPM-2/clusterin can be antisense oligonucleotides. The active method step of each of these methods is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat a non-cancerous angiogenesis-related disease or reduce angiogenesis in a non-cancerous angiogenesis-related disease and enhance the chemo- or radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the instant Application are also claimed in the '395 application.

33. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.
>
> (g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sensibar et al. (Cancer Research, 55, 2431-2437, 1995, cited on PTO 1449 filed January 9, 2002).

34. Sensibar et al. disclose phosphorothioate antisense oligonucleotides fully complementary to a nucleic acid encoding Sulfated glycoprotein-2 (an alternative name for TRPM-2), including the translation initiation codon. This sequence is identical to that designated as SEQ ID NO: 5 in the instant application. When transfected into LNCaP cells (a human prostate cancer cell line), these antisense oligonucleotides resulted in a

decline of SGP-2 synthesis, indicating that expression of SGP-2 was inhibited (see pages 2433-2435, section entitled "Effect of Antisense Oligonucleotides to SGP-2 on LNCaP Cells"). Although Sensibar et al. do not disclose that their oligonucleotides delay progression of prostatic tumor cells to an androgen independent state or enhance the chemo- or radiation sensitivity of cancer cells, the antisense compositions of Sensibar et al. meet all of the limitations of the compositions claimed in claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27 and, therefore, would be expected to delay the progression of prostatic tumor cells to an androgen independent state or enhance the chemo- or radiation-sensitivity of a cancer cell.

35. Furthermore, since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "delay progression of prostatic tumor cells to an androgen independent state" or to "enhance the chemo- or radiation sensitivity of cancer cells" as claimed, absent evidence to the contrary. See, for example, MPEP 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 USC 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 USC 103 and for anticipation under 35 USC 102' *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms

of function, property or characteristic. Therefore, a 35 USC 102/103 rejection is appropriate for these types of claims as well as for composition claims."

36. Therefore, Sensibar et al. anticipate claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27.

37. Claims 1, 3, 6, 9, 14, 15, 18, 21, 24, 26, 29 and 30 are directed to an invention not patentably distinct from claims 2-4, 6, 10 and 11 of commonly assigned application 10/080,794. Specifically, claim 2 of the '794 application is fully encompassed within claims 1 and 3 of the instant Application, claim 3 of the '794 application is fully encompassed within claims 6 and 9 of the instant Application, claim 4 of the '794 application is fully encompassed within claims 29 of the instant Application, claim 6 of the '794 application is fully encompassed within claims 14, 15, 21 and 30 of the instant Application, claim 10 of the '794 application is fully encompassed within claims 18 of the instant Application and claim 11 of the '794 application is fully encompassed within claims 24 and 26 of the instant Application.

38. Claim 18 is directed to an invention not patentably distinct from claim 1 of commonly assigned application 09/967,726. Specifically, claim 18 is identical to claim 1 of the '726 application.

39. Claims 1-11, 18 and 24-28 are directed to an invention not patentably distinct from claims 1-3 and 9 of commonly assigned application 10/646,391. Specifically, the active step of each method in these applications is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat melanoma and enhance the chemo- or

radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the instant Application are also claimed in the '391 application.

40. Claims 1-11, 18 and 24-28 are directed to an invention not patentably distinct from claims 1-3 and 6-8 of commonly assigned application 10/828,394. Specifically, the active step of each method in these applications is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat a cancerous angiogenesis-related disease or reduce angiogenesis in a cancerous angiogenesis-related disease and enhance the chemo- or radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the instant Application are also claimed in the '394 application.

41. Claims 1-11, 18 and 24-28 are directed to an invention not patentably distinct from claims 1-3 and 6-8 of commonly assigned application 10/828,395. Specifically, the active step of each method in these applications is reduction of clusterin/TRPM-2 and performing this step would necessarily both treat a non-cancerous angiogenesis-related disease or reduce angiogenesis in a non-cancerous angiogenesis-related disease and enhance the chemo- or radiation sensitivity of a cancer cell. Additionally, the claimed SEQ ID NOS: 4, 5 and 12 of the instant Application are also claimed in the '395 application.

42. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned applications 09/967,726, 10/080,794, 10/646,391, 10/828,394 and 10/828,395, discussed above, would form the basis for a rejection of

the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

43. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 13 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sensibar et al. as applied to claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27 above, and further in view of Benner et al. (Journal of Pharmacological and Toxicological Methods, cited on IDS of January 9, 2002).

44. Claims 12 and 13 limit claim 8 and claim 31 limits claim 10 by stating the method of claim 8 can be performed in combination with a chemotherapeutic agent and that the chemotherapeutic agent can be a taxane or mitoxanthrone.

45. Sensibar et al. teach phosphorothioate antisense oligonucleotides fully complementary to a nucleic acid encoding Sulfated glycoprotein-2 (an alternative name for TRPM-2), including the translation initiation codon. One of the sequences taught by Sensibar et al. is identical to SEQ ID NO: 5 of the instant application. When transfected into LNCaP cells (a human prostate cancer cell line), these antisense oligonucleotides resulted in a decline of SGP-2 synthesis, indicating that expression of SGP-2 was inhibited (see pages 2433-2435, section entitled "Effect of Antisense Oligonucleotides to SGP-2 on LNCaP Cells"). Although Sensibar et al. do not disclose that their oligonucleotides delay progression of prostatic tumor cells to an androgen independent state or treat prostrate cancer in an individual, the antisense compositions of Sensibar

et al. meet all of the limitations of the compositions claimed in claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27 and, therefore, would be expected to delay progression of prostatic tumor cells to an androgen independent state or treat prostrate cancer in an individual. Sensibar et al. do not teach use of these phosphorothioate antisense oligonucleotides in combination with another chemotherapeutic agent in cancer cells.

46. Benner et al. teach that antisense therapy can be used in combination with traditional chemotherapy methods in hematological cancers. Benner et al. teach that this combination offers the potential of requiring lower doses of chemotherapy agents that would lower the side effects associated with chemotherapy.

47. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use antisense oligonucleotides targeted to SGP-2 as taught by Sensibar et al. in combination with traditional chemotherapeutic agents as taught by Benner et al. A person of ordinary skill in the art would have been motivated to do so and would have had a reasonable expectation of success in using oligonucleotides targeted to SGP-2 taught by Sensibar et al. in combination with traditional chemotherapy agents to treat cancer because Sensibar et al. teaches that these oligonucleotides successfully inhibit expression of SGP-2 in a cancer cell that expresses SGP-2 and because Benner et al. teach the potential benefits to be derived from combining antisense therapy with traditional chemotherapy agents. Further, Section 2144.06 of the MPEP states the following in the context of "art recognized equivalence for the same purpose":

> "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in

the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

48. Therefore, the invention of claims 12, 13 and 31 would have been obvious, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 22, 2004

SEAN McGARRY
PRIMARY EXAMINER
1635